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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/022,390	12/17/2001	Manuel Vega	17109-003001	5547

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EXAMINER
POPA, ILEANA

ART UNIT	PAPER NUMBER
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/022,390	VEGA ET AL.	
	Examiner	Art Unit	
	Ileana Popa	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45,46,62,70,78,94 and 96-100* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45,46,62,70,78,94 and 96-100* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/03/2006 has been entered.

Note: Change of Examiner

The Examiner of record is now Ileana Popa, Art Unit 1633. Therefore, future correspondence should reflect such changes. Also, at the end of the Action is the information regarding the SPE and the Art Unit.

2. Claims 1-44, 46-61, 63-69, 71-77, 79-93, and 95 have been cancelled. Claims 96-100 are new.

Claims 45, 46, 62, 70, 78, 94, and 96-100 are pending and under examination.

**It is noted that the instant claims are under examination only with respect to the mutation identified in claim 62 as "T to N at position 350", represented by SEQ ID NO: 113.

Claims 45, 46, 62, 70, 78, 94, and 96-100 contain non-elected subject matter.

Since no generic or linking claim is found allowable, Applicant is required to amend the

claims such that they reflect the elected species.

3. Applicant traverses the species election requirement between the SEQ ID NOs recited in claim 96 on the grounds that the mutations are all in Rep proteins encoded by overlapping nucleic acids and therefore, all mutations are in the same gene, the gene that encodes the Rep proteins. The traversal is on the ground(s) that MPEP 803.04 allows for the examination of up to ten sequences in a single examination without restriction. Applicant argues that, since the claimed mutations are all in the same protein, they should be examined together because one search of the gene should cover all mutations. This is not found persuasive because the claimed SEQ ID NOs represent different mutations and therefore, independent proteins encoded by different nucleic acids that require distinct searches. Moreover, it is noted that, since the addition of the guidelines to the MPEP, the biological sequence databases required to be searched for the examination of any biological sequence have grown tremendously, and thus the Technology Center no longer routinely examines and searches more than one independent biological sequence for any single application.

With respect to the argument that the species were elected for search purpose only and that the Examiner should search additional species if no art is found until a reasonable number of species is searched, it is noted that this is true only if the genus is allowable. In this instance, the genus is not allowable (see below).

For the reasons above, the requirement for species election is deemed proper and it is made final.

Claim Rejections - 35 USC § 101

4. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. Claims 45, 46, and 62 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The instant claims are drawn to a nucleic acid molecule that encodes a mutant adeno-associated virus (AAV) Rep protein and to a cell comprising the said nucleic acid molecule. Claims 45, 46, and 62 do not sufficiently distinguish over mutant AAV encoding a mutant Rep protein or cells that exist naturally within an animal body and that are infected with the mutant AAV encoding a mutant Rep protein; the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. Therefore, claims 45, 46, and 62 encompass a naturally occurring virus and a naturally occurring cell infected by the virus within an animal body. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "Isolated" or "Purified". See MPEP 2105.

In addition to the above, claim 46, as written, encompasses human cells that exist naturally within a human; the term “cell” is not defined by the specification and therefore, the cell can be present in a human being and be an inseparable part of the human being itself. The scope of the claim, therefore, encompasses a human being, which is non-statutory subject matter.

Claim Rejections - 35 USC § 112, 2nd paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

7. Claim 45 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is not clear what Applicant means by "replication in a host cell of virus, in its genome", i.e., it is not clear whether the Applicant means the cell genome or the viral genome. Additionally, it is not clear what "the equivalent position" is. Positions in a nucleic acid can be structurally equivalents or they can be functionally equivalents. Since the metes and bounds of the claim cannot be determined, the claim is indefinite.

Claims 46, 62, 70, 78, 94, and 96-100 are rejected for being directly or indirectly dependent from the rejected claim 45.

8. Claims 62 and 96 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is not clear what "the corresponding residues" or "corresponding codons" in the other serotypes are, because a corresponding residue/codon can mean a residue/codon at the same position within the protein or a residue/codon in a corresponding functional domain that is not necessarily in the same position. Since the metes and bounds of the claim cannot be determined, the claim is indefinite.

Claims 70, 78, and 94 are rejected for being directly or indirectly dependent from the rejected claim 62. Claims 99 and 100 are rejected for being dependent from the rejected claim 96.

9. Claim 96 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 96 recites the limitation "AAV-7" or “corresponding codon replacements” in claim 45. There is insufficient antecedent basis for this limitation in the claim.

Claims 99 and 100 are rejected from being dependent from the rejected claim 96.

10. Claim 96 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is apparent that the instant claim is drawn to distinct of nucleic acids, however, it is not clear from the language of the claim whether Applicant recites them in alternative, combination, or all together. Additionally it is not clear from the language of the claim what Applicant means by “corresponding codon replacements”. The metes and bounds of the claim cannot be determined and the claim is indefinite.

Claims 99 and 100 are rejected from being dependent from the rejected claim 96.

Claim Rejections - 35 USC § 112, new matter

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 96, 99, and 100 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 96, 99, and 100 are rejected because a nucleic acid molecule encoding Rep protein from AAV-7 is not enabled by the disclosure. It is noted that the new claims to claims introduce new matter. Applicants assert that support for the new claims can be found in the table spanning pages 53-71. This is not found persuasive. The table discloses amino acid sequences of exemplary mutant proteins, without mentioning the AAV-7 serotype. The specification disclose that the AAV serotypes include, but are not limited to, AAV-1, 3, 3B, 4, 5, and 6. Although the specification teaches that the serotypes are not limited to the ones mentioned above, the specification does not provide any disclosure, suggestion, or motivation to particularly pick AAV-7 from the remaining serotypes and therefore there is only support in the specification for the AAV-1, 3, 3B, 4, 5, and 6 serotypes.

Claim Rejections - 35 USC § 112, written description

13. Claims 45, 46, 62, 70, 78, 94, and 96-100 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description Requirement" makes it clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosures of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

Applicant argues that the fact that the specification does not describe or list all mutant species that result in an increased titer is not a basis for rejection under written description. Applicant argues that the written description requirement is met by disclosing of sufficiently detailed, relevant identifying characteristics, such as complete or partial structure or functional characteristics when coupled with a known or disclosed

correlation between function and structure. Applicant submits that the standard is met in the instant case because the specification describes eight such mutants and provides formulae for mutant proteins for all loci. Moreover, as amended, the claims recite the highly related AAV serotypes, wherein the amino acid sequences encoded by the nucleic acids are highly conserved and wherein the introduction of the claimed mutations renders the sequences even more similar. In view of the disclosure, one of skill in the art could envision the sequences for all of the claimed serotypes at the time of filing and therefore, Applicant possessed the claimed species at the time of filing. Applicant concludes that the mere fact that the disclosure specifies eight mutations, seven different serotypes, and means for producing and testing additional mutant Rep proteins and nucleic acids encoding them is evidence of the possession of the entire genus, as claimed.

Contrary to Applicant's assertion, he was not in possession of the full genus for the following reasons:

Claims 45, 46, 62, 70, 78, 94, and 96-100 are drawn to nucleic acid molecules encoding mutant AAV proteins with increased activity, wherein the increased activity results in increased virus titer. Therefore, claims 45, 46, 62, 70, 78, 94, and 96-100 encompass a wide and variable genus of nucleic acid molecules the structure of which is not sufficiently disclosed in the specification and the claims.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably conclude the inventors had possession of the claimed invention. Such possession may

be demonstrated by describing the claimed invention with all its limitations using such descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention. Possession may be shown by an actual reduction to practice, showing that the invention was "ready for patenting", or by describing distinguishing identifying characteristics sufficient to show that the Applicants were in possession of the claimed invention (January 5, 2001, Fed. Reg., Vol. 66, No. 4, pp.1099-11).

In analyzing whether the written description requirement is met for the genus claims, it is determined whether representative numbers of species have been described by their complete structure and functional characteristics.

When the claims are analyzed in light of the specification, the mutant nucleic acid can be any nucleic acid encoding a mutant Rep protein, as long as the Rep protein has increased activity (p. 9, paragraph 0111, p. 10, 0133, p. 16, paragraphs 0195-0200, p. 23, paragraph 0208). The genus of proteins nucleic acids encoding for mutant Rep proteins is very large; and a great deal of variability is encompassed by the instant claims. The instant claims encompass in their breadth any nucleic acid encoding for a mutant Rep protein that has increased activity. With the exception of the sequences disclosed eight mutations, the specification fails to describe additional representative species of the nucleic acids mentioned above. The genus (i.e., the nucleic acids encoding for mutant Rep proteins) is described by its function to affect viral replication, but the specification does not provide any disclosure as to what would have been the complete structure of sufficient number of species of the claimed genus. Additionally,

the specification does not describe what would have been the identifying characteristics, such as specific features and functional attributes, of the different nucleic acids. Applicant has not provided any information besides the characterization of the genus as having increased activity, wherein the increased activity results in increased viral replication. This limited characterization, however, does not indicate that the Applicant had possession of the claimed genus of modified nucleic acids. Applicant is relying upon biological activity and the disclosure of eight mutants having increased activity to support an entire genus. It is well known that minor structural differences among even highly structurally related compounds can result in substantially different biology. The specification fails to disclose what requirements a nucleic acid must meet to encode a mutant Rep protein with increased activity, i.e., the specification fails to provide the relationship between structure and function for the nucleic acids encoding the mutant proteins. The specification does not contain any disclosure of the structure of all variants. One skilled in the art would know that a change of even one amino acid residue in the claimed sequences could render an inactive protein or a protein with a diminished activity. Therefore, Applicant has not disclosed the requisite structural features of the protein that result in the disclosed increased activity, a feature deemed essential for the instant invention. Therefore, one of skill in the art would not recognize Applicant to be in possession of the entire genus of nucleic acids encoding a mutant Rep protein. Applicant argues that as amended, the claims recite highly related AAV serotypes, wherein the amino acid sequences encoded by the nucleic acids are highly conserved and that the introduction of the claimed mutations renders the sequences

even more similar. Consequently, Applicant argues, one of skill in the art could envision the sequences for all of the claimed serotypes at the time of filing and therefore, Applicant possessed the claimed species at the time of filing. The instant claims recite that the claimed mutations (i.e., in the Rep78 of the AAV-2 serotype) are introduced at the corresponding residues in the other serotypes, and the specification defines that a corresponding residue refers to an amino acid position based upon alignment to maximize sequence identity, as demonstrated in Fig. 3 A and B (p. 6, paragraph 0071). However, it is clear from Fig. 3 A and B that the different Rep proteins of the different serotypes have different lengths and therefore, since the "corresponding residue" does not have the same position in all proteins, it is unclear that the claimed mutations would result in the same activity. The art teaches that Rep proteins are divided into partially distinct functional domains that are spread throughout the protein length and that most mutations disrupt Rep function (Gavin et. al., J Virol, 1999, 73: 9433-9445, p. 9433, column 2), and since the length for the different Rep proteins is not the same, one of skill in the art would not expect that the same amino acid substitution at different positions in the proteins would result in the same activity. Therefore, contrary to Applicant's assertion, the mere fact that the disclosure specifies eight mutations is not evidence that Applicant was in possession of the entire genus, at the time of filing. While it is true that Applicant provides means for producing and testing additional mutant Rep proteins and nucleic acids and this can be accomplished by routine experimentation, the fact that one of skill in the art would require additional experimentation is a proof that applicant was not in possession of the claimed genus.

In conclusion, this limited information is not sufficient to reasonably convey to one of ordinary skills in the art that the Applicant invented what was claimed. Consequently, the Applicant was not in possession of the instant claimed invention, at the time the application was filed.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 45, 46, and 94 are rejected under 35 U.S.C. 102(b) as being anticipated by Gavin et al.

Gavin et al. teach a nucleic acid encoding a mutant AAV-2 Rep78, wherein mutant Rep protein has increased activity and wherein co-transfection of the nucleic acid encoding the mutant Rep and recombinant AAV plasmid into 293 cells mediates increased viral replication as compared to the wild type Rep(i.e., increased recombinant AAV titer upon introduction of the virus into the host cell) (p. 9434, column 2, p. 9435, column 1, p. 9436, column 2, Fig. 3). Since Gavin et al. teach all the limitation of the instant claims, the claimed invention is anticipated by the above-cited art.

16. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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